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AN OXYGEN TOXICITY COMPUTER.(U)
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An Oxygen Toxicity Computer

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SUMMARY

Operational Problem.

Clinical and operational use of hyperbaric oxygen is currently limited by fixed exposure values published in the *U. S. Navy Diving Manual*. These published limits do not take into consideration the prior exposure history of an individual, do not allow for fluctuating oxygen partial pressures, and do not provide the operational personnel the flexibility that is physiologically possible.

Technical Objective.

This investigative effort was undertaken to explore the feasibility of developing an oxygen exposure computer for tracking an individual's hyperbaric oxygen exposure and estimating the toxicity risk at any point in time.

Approach.

A survey of the literature was performed to locate experimental data on time limits for human exposures to various oxygen partial pressures. Animal experiments were performed to evaluate a time weighted average metric for quantifying oxygen exposure. Finally mathematical algorithms were developed for estimating human oxygen toxicity risk based upon the best information presently available.

Results.

* Animal experiments seem to indicate that a time weighted average can be used for evaluating an accumulative oxygen exposure.
* Data on human exposure limits published in the scientific literature is extremely variable and is subject to influences, both physiological and environmental, that are hard to control in operational settings.
* Algorithms were developed based upon the best scientific information presently available and were used in a computer model designed to aid clinicians in assessing the risk of oxygen toxicity during hyperbaric oxygen exposures.

Conclusions.

The development of an oxygen exposure computer seems to be very feasible and desirable for extending operational flexibility. Critical elements needed in this development are: improved human data on oxygen exposure limits and validation of the time weighted average as a metric for evaluating human oxygen exposure history.

BACKGROUND

It is well recognized that elevated oxygen partial pressures can be used advantageously in a number of operational and clinical settings. Operationally oxygen has been used in closed circuit breathing apparatus to ensure that underwater swimmers are undetected during clandestine operations. It has also been used to reduce the risk of decompression sickness and decrease the time required for decompression. Clinically hyperoxia has been used in the treatment of decompression sickness, air emoblism, carbon monoxide and carbon dioxide poisoning, gas gangrene, and osteomyelitis. There are probably additional conditions in which oxygen can be advantageously used, but supportive research is lacking.

The beneficial use of high partial pressures of oxygen is limited both operationally and clinically by its acute and chronic toxicity. As Clark (3) has pointed out, the poisoning effects of oxygen have an impact on every living cell. "Given sufficient duration of exposure, a toxic inspired PO_2 will cause functional disruption and cellular damage in any organ system of the body. The specific manifestations of 0_2 poisoning that limit the safe duration of hyperoxia vary with the level of PO_2 and the presence of other factors ..."

The two most widely recognized effects of oxygen poisoning occur in the pulmonary and central nervous systems. Paul Bert (2) first observed symptoms of oxygen poisoning in the nervous system of lower animals. He reported that at high oxygen partial pressures convulsions occurred with little warning after only a very short exposure. J. Lorrain Smith (14) followed with the observation that animals exposed to moderately high tensions of oxygen over prolonged periods suffered severe and finally fatal pulmonary damage. Numerous studies followed in which both animals and humans exposed to hyperoxia produced similar or analogous results.

An active part of the oxygen research program has been devoted to identifying ways of reducing, delaying and eliminating its toxic effects. A number of drugs have been evaluated and found unsatisfactory (6). The one generally accepted and now routinely applied technique for postponing oxygen toxicity is the systematic alteration of the PO_2 level. This intermittency technique was first described by Lambertsen (10) and has subsequently been researched by Penrod (13), Clark (3), Hall (7), Paegle *et al.* (12), and others. The general conclusion from all of this work has been that intermittency of high and low oxygen partial pressures greatly extends oxygen tolerance. The underlying mechanism at work during the intermittent oxygen exposure has not been identified and the utilization of intermittency, although extending the acceptable dose range, seems to have complicated our understanding of acceptable exposure limits. Previously accepted limits for continuous exposures similar to those shown in Figs. 1 and 2 now have to be recalculated to accommodate fluctuating oxygen exposures.

Assessment of Oxygen Risk.

The risk of oxygen toxicity during operational use varies greatly depending on the extent of the exposure and a number of potentiating factors such as elevated alveolar and tissue carbon dioxide, exercise, immersion, gas density, and temperature just to mention a few. A further complication in the use of oxygen is that tolerance both between and within individuals, is not presently predictable. Attempts to correlate oxygen tolerance with age, height, weight, physical fitness, athleticism, smoking, ingestion of alcohol, psychological health and personality traits have failed (5). The best we can do at present is describe the oxygen

toxicity phenomena and estimate the risk associated with a continuous exposure. Having restricted knowledge based on continuous exposures is a limiting factor in the application of this information and has forced us to adopt rigid limits on the use of oxygen and restricted the flexibility of field personnel.

Operations with Restrictive Limits.

The U. S. Navy's operational use of oxygen is limited by fixed exposure values published in the *U. S. Navy Diving Manual*. No attempt is made to provide operators or clinicians in the field with the flexibility to assess the risk of oxygen toxicity against the requirements of their operation. For example, an underwater demolition team (UDT) swimmer making a clandestine swim into an unfriendly harbor using a closed circuit oxygen rebreather, if confronted by a mine defense net, would not be authorized to dive deeper than 40 feet to go under it. However, a short, deeper dive may do little to alter his oxygen toxicity risk.

A clinical example, often encountered in the treatment of CNS decompression sickness, involves the patient who upon reaching the end of the 60 foot oxygen breathing period during a Navy oxygen treatment table 6, still has residual symptoms. The physician would like to extend the treatment and give the patient the benefit of additional oxygen time, but the *U. S. Navy Diving Manual* only allows for one additional oxygen period. How does he evaluate the risk associated with such a decision? It would be helpful in both of these operational situations if the field personnel had available to them a calculation device for estimating the risk associated with their decisions rather than a fixed restrictive limit.

Calculation of Oxygen Exposure.

In 1968 Hills and Bossett (9) suggested what they termed the principle of superposition for integrating the effects of fluctuating oxygen levels. With this principle they proposed that acute oxygen toxicity is additive with respect to oxygen partial pressure but not with respect to time. They produced a demonstration of their superposition principle using six rats (Fig. 3). The results provided impressive support for the concept and stimulated Hills (8) to develop an oxygen dose calculator. The calculator was used to tabulate an oxygen exposure history in terms of a Cumulative Oxygen Toxicity Index (COTI). Perhaps the biggest disadvantage of the Hills approach is that the index is not directly interpretable in terms of oxygen partial pressures and the existing time limits for continuous exposures. The major contribution of this work lies in its demonstration that the toxic effects of various serially presented oxygen partial pressures are related in a linear fashion. This latter finding led Berghage (1) to explore the use of a time-weighted average as an oxygen exposure index. The author exposed over 200 rats to various intermittency schedules (Table I). Time weighted averages were calculated for each fluctuating exposure and compared with results obtained from continuous oxygen exposures. The results are shown in Fig. 4. Although there is a great deal more variability in the fluctuating oxygen exposure data compared with the continuous exposures, the mathematical descriptions of the two relationships are very much alike.

Relationship Between Oxygen Partial Pressure and Time of Onset of Convulsions for 50% of the Exposed Animals

Continuous Oxygen Exposures	Time-Weighted Average of Fluctuating Oxygen Exposure
$y = -183.34 + \frac{1122}{X}$	$y = -189.96 + \frac{1141}{X}$
r = .98	r = .84
SE = 30.6	SE = 48.6
F = 157.12	F = 53.7

y = Time to convulsions for 50% of the animals

X = Partial pressure of oxygen
(measured for the continuous exposures)
(time-weighted average PO_2 for the fluctuating exposures)

r = Correlation coefficient (Pearson product moment)

SE = Standard error of the estimate

F = Measure of statistical significance

Similar results have been obtained in our analysis of the data presented by Clark (3), Hall (7), and Hills (8). The correlations between the time-weighted average oxygen partial pressure and time of onset of oxygen toxicity symptoms for these three studies are well above that obtained in the Berghage (1) study. The respective correlation coefficients are .98, .98, and .99. The results of all of these studies seem to support the idea that a time-weighted average oxygen partial pressure can be utilized as a means of assessing the magnitude of an intermittent oxygen exposure.

The animal studies described above may have provided the bridge necessary for the utilization of available oxygen toxicity data. Being able to calculate an oxygen dose across a fluctuating oxygen exposure allows one to take existing scientific literature and utilize it in an operational setting. Having the calculated dose in a form that does not require a special translation or conversion for interpretation is an important feature of this approach. Finally, it is essential that the information on oxygen toxicity be presented in a risk probability form as opposed to a fixed limit, thus giving the individual at the scene the flexibility he/she needs to carry out the operation. A flow diagram for such a calculating system is shown in Fig. 5.

An Oxygen Toxicity Computer (OTC).

Recent advances in microprocessors have made possible the accomplishment of all of the objectives described above. The critical element in the development and acceptance of an OTC is the acceptance of the time-weighted average as a measure of oxygen exposure. Existing animal studies support this concept, but human data is needed for verification. The only way to obtain the needed human data with the current prohibition on human experimentation is to build the OTC and put it into the field as a monitoring device. Toward this end we have conducted an extensive review of the scientific literature on human hyperbaric oxygen exposures (4,5,11,15). The data from the scientific literature were analyzed using the principle of the time-weighted average PO_2. From this analysis two sets of equations were derived: one for the clinical setting in which a resting subject is in a dry chamber environment and the other for the operational setting in which the subject is immersed and

exercising. For the clinical setting the following information is estimated:

(1) the probability of central nervous system (CNS) toxicity occurring given the present exposure history;

(2) the time remaining before a major increase in the probability of CNS symptoms;

(3) the likely reduction in vital capacity that the patient is experiencing with a given exposure history, and

(4) the time remaining before the patient may reach a debilitating level of pulmonary oxygen toxicity.

The estimations for the operational setting are limited to CNS symptoms (items (1) and (2) above) because of the operational dive profiles involved.

The microprocessor device shown in Fig. 6 was selected for use as the OTC because it is small, readily portable, and provides the programming flexibility which will allow updating of the calculation algorithms as more information becomes available. As we learn more about the underlying oxygen toxicity mechanisms, we will be able to improve the estimates provided by the OTC and sharpen our use of the hyperbaric oxygen tool.

With this type of information available, the operational personnel in the field can evaluate the risks associated with their current situation and alter their pressure, time, and gas mixture profile to stay within acceptable risk limits.

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TABLE 1

Time To Convulsions for 50% of the Animals
Exposed to Various Intermittency Schedules

High Oxygen Partial Pressure (ATA)	Time on High Oxygen Partial Pressure (Minutes)	Time on Low Oxygen Partial Pressure (PO_2=.5 ATA) (Minutes)	Time to Convulsions for 50% of the Animals (Minutes)
3.2	Continuous	0	140
3.2	15	1	302
3.2	15	5	344
3.2	15	10	353
3.2	40	1	265
3.2	40	5	310
3.2	40	10	295
3.2	80	1	249
3.2	80	5	239
3.2	80	10	220
3.9	Continuous	0	93
3.9	15	5	192
3.9	15	10	225
3.9	40	5	143
3.9	40	10	157
3.9	80	5	67
3.9	80	10	138
4.2	Continuous	0	56
4.2	15	1	158
4.2	15	5	247
4.2	15	10	215
4.2	15	20	230
4.2	40	1	64
4.2	40	5	143
4.2	40	10	117

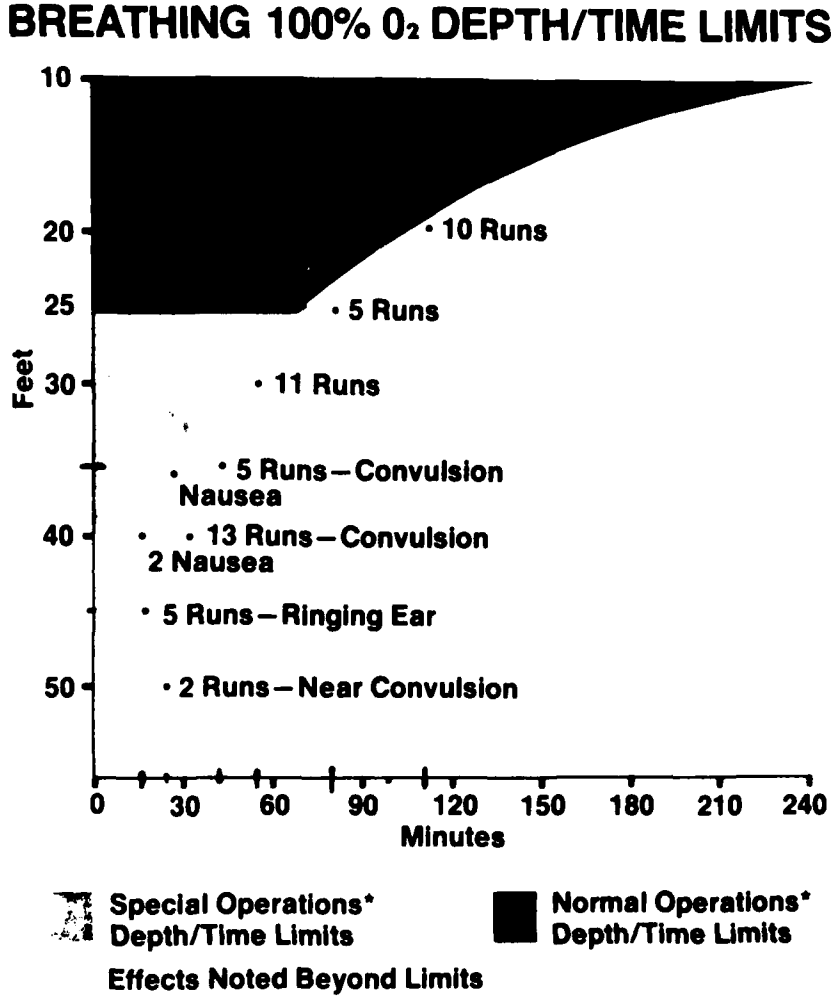

Fig. 1. - Central Nervous System toxicity limits for continuous exposure to hyperbaric oxygen while immersed and exercising. (U. S. Navy Diving Manual)

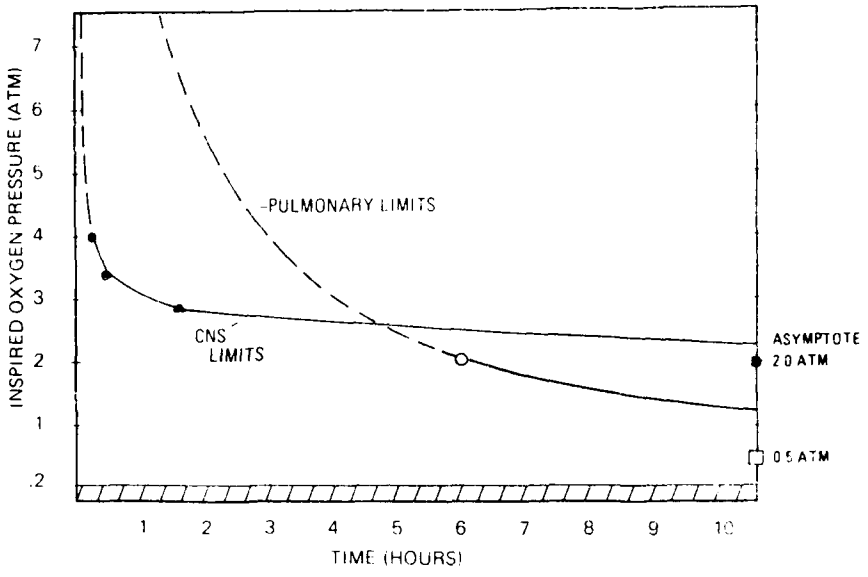

Fig. 2. - Central Nervous System and pulmonary toxicity limits for continuous exposure to hyperbaric oxygen for dry resting subjects. (Clark and Lambertsen, 1971)

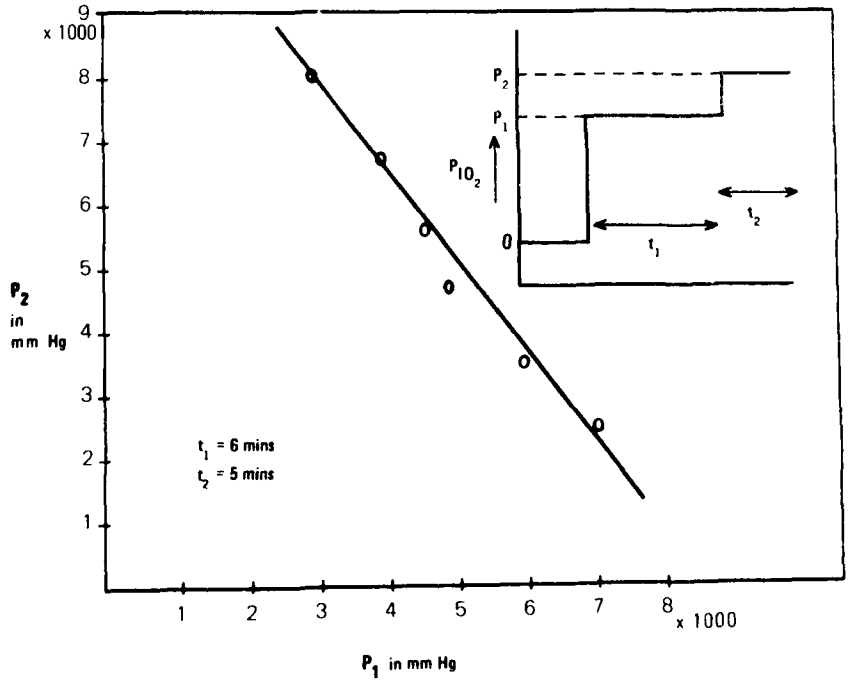

Fig. 3. - The relationship between consecutive exposures to pure oxygen (6 minutes at P_1 followed by 5 minutes at P_2) for equal onset time of convulsions in 6 rats. (Hills, 1976)

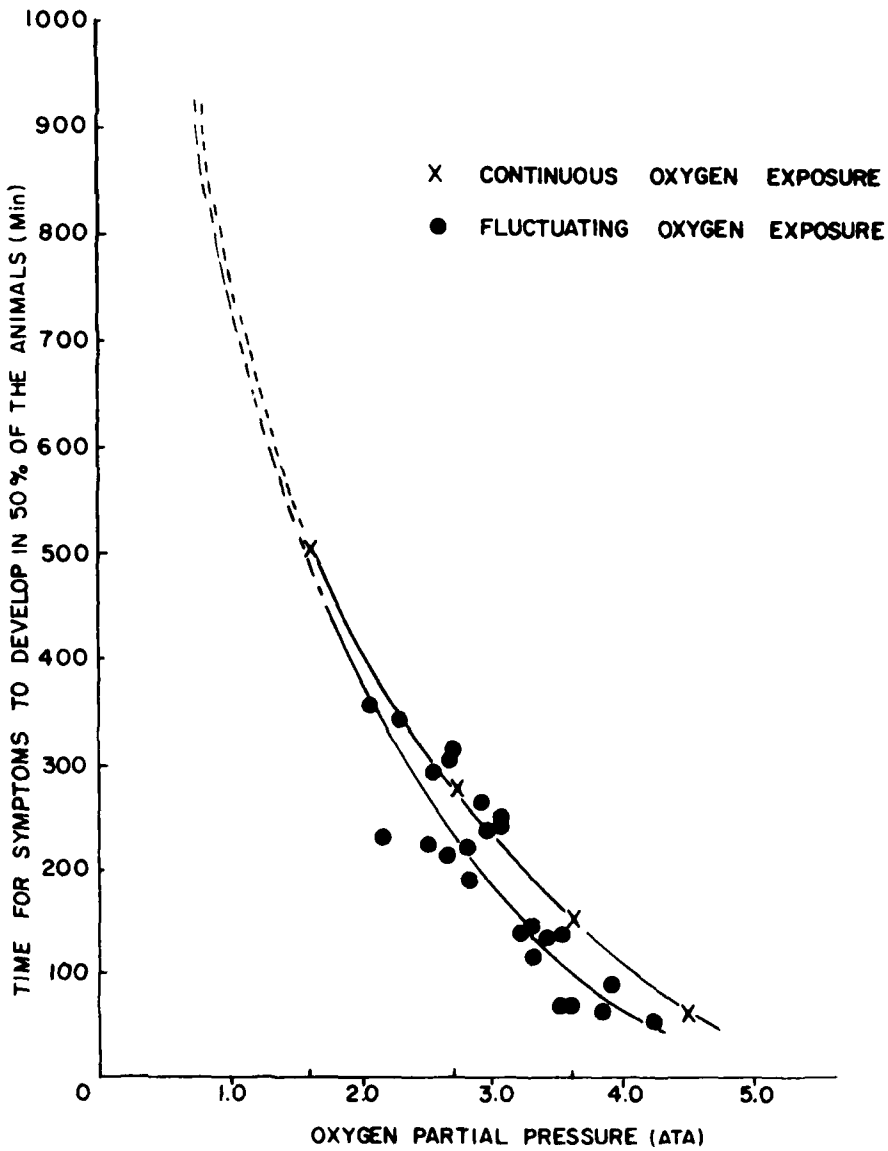

Fig. 4. - The relationship between a time-weighted oxygen exposure calculation and the onset time for 50% of the exposed animals.

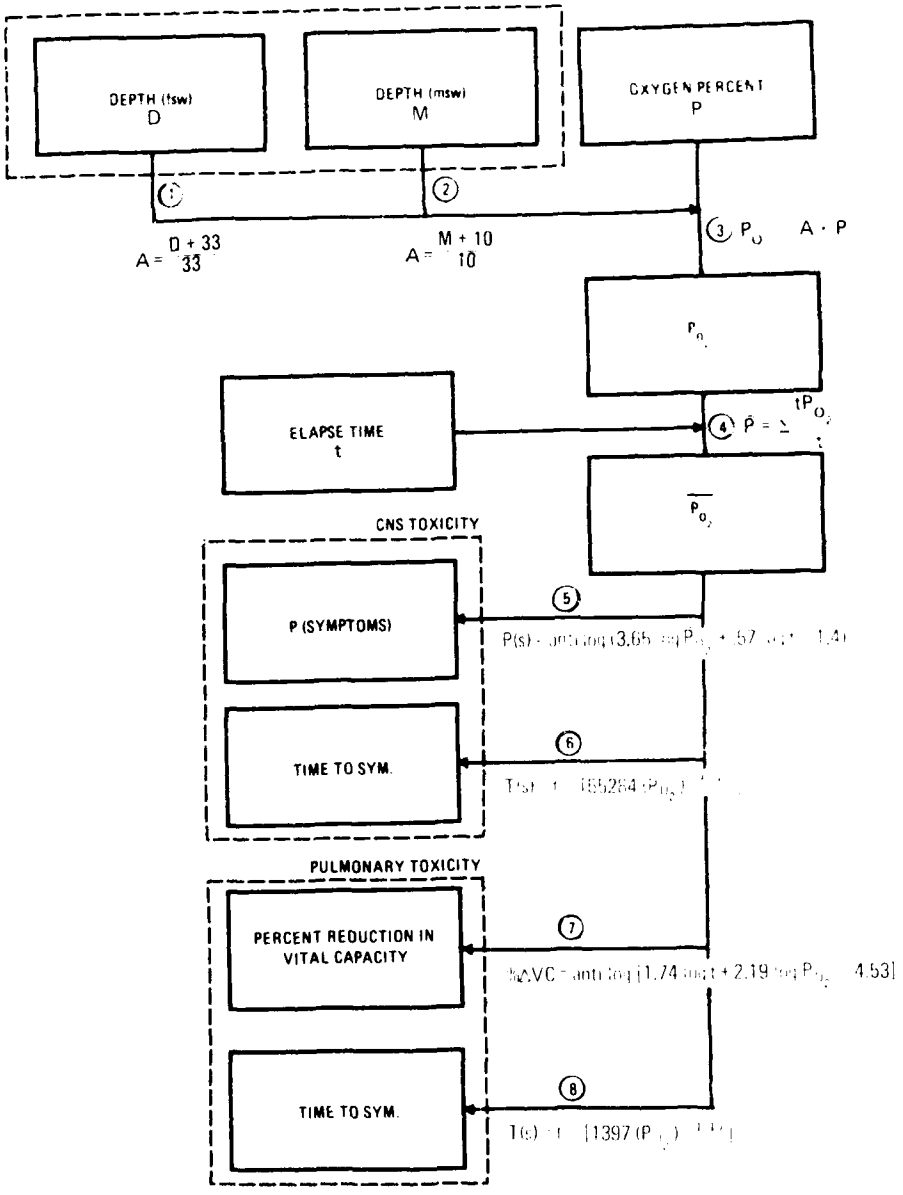

Fig. 5. - Block diagram for calculating the risk of oxygen toxicity occurring during a hyperoxic chamber exposure.

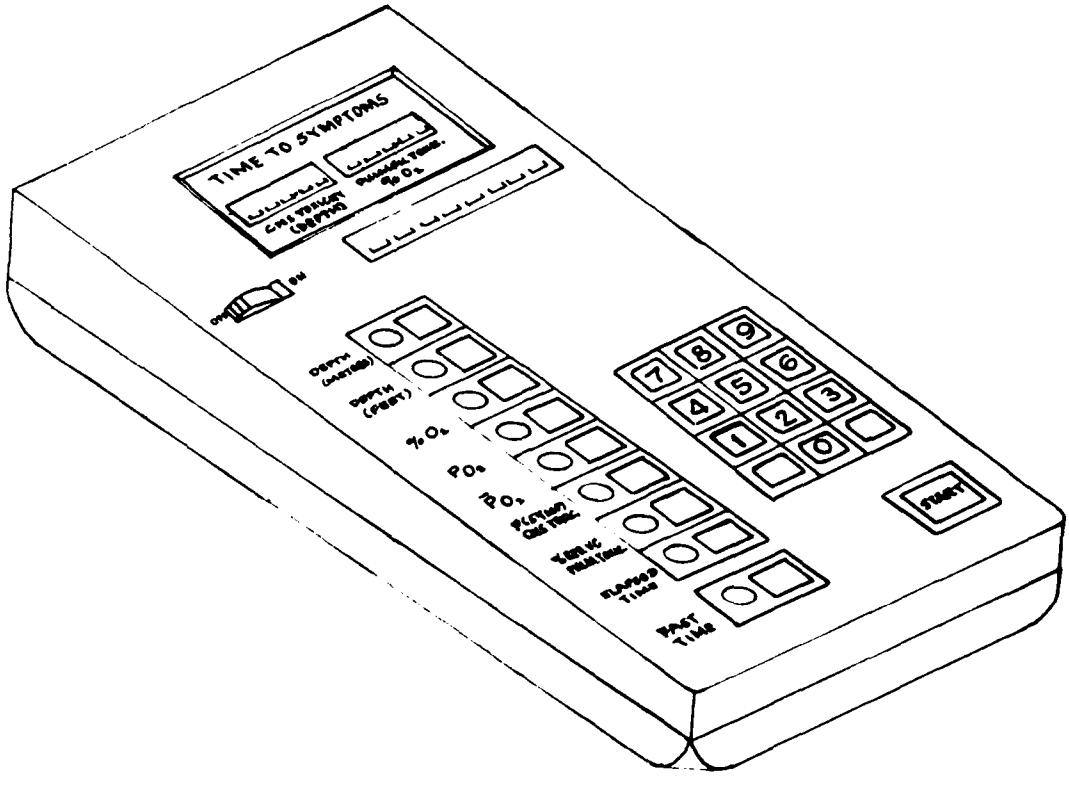

Fig. 6. - Conceptual design for an oxygen toxicity computer.

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20. ABSTRACT *(Continue on reverse side if necessary and identify by block number)*

(U) Despite the availability of oxygen toxicity data in the scientific literature clinicians in the field employing hyperbaric oxygen have only a vague idea of the time-pressure limits for oxygen exposures. A joint development program between the Naval Health Research Center and the Naval Ocean Systems Center has produced a prototype Oxygen Toxicity Computer (OTC). This small hand-held device can be used to track the course of a hyperbaric oxygen treatment and provide the attending physician with information on

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(a) the probability of central nervous system toxicity, (b) the time remaining before a major increase in the probability of central nervous system symptoms, (c) the likely reduction in vital capacity, and (d) the time remaining before reaching a debilitating level of pulmonary oxygen toxicity. With this information available the attending physician can alter his pressure-time-breathing medium profile to stay within acceptable risk limits.


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